PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Monitoring multidimensional aspects of quality of life after cancer immunotherapy: protocol for the international multi-centre, observational QUALITOP cohort study
AUTHORS	Vinke, Petra; Combalia, Marc; de Bock, Geertruida H.; Leyrat, Clémence; Spanjaart, Anne; Dalle, Stephane; Gomes da Silva, Maria; Fouda Essongue, Aurore; Rabier, Aurélie; Pannard, Myriam; Jalali, Mohammad; Elgammal, Amal; Papazoglou, Mike; Hacid, Mohand-Said; Rioufol, Catherine; Kersten, Marie-José; van Oijen, Martijn; Suazo-Zepeda, Erick; Malhotra, Ananya; Coquery, Emmanuel; Anota, Amélie; Preau, Marie; Fauvernier, Mathieu; Coz, Elsa; Puig, Susana; Maucort-Boulch, Delphine

VERSION 1 – REVIEW

REVIEWER	Zarogoulidis, P. Aristotle Univ Thessaloniki
REVIEW RETURNED	18-Oct-2022

GENERAL COMMENTS	An excellent manuscript in its field, I have no corrections

REVIEWER	Goodman, Michael Emory University Rollins School of Public Health, Epidemiology
REVIEW RETURNED	19-Jan-2023

GENERAL COMMENTS	Thank you for the opportunity to review this paper. Although the idea of creating a multicenter cohort of immunotherapy patients is praiseworthy, the description of the proposed study methods is somewhat vague. Below, I am offering a few suggestions that in my opinion will strengthen this paper. 1. I am afraid that a reader who only has time to review the abstract will come away without a clear understanding of the study design and its methods. For example, the abstract lacks a clear explanation of is meant by “a tailored questionnaire completed at regular intervals”, and the actual methods of data analysis are not mentioned. 2. Section on Patient Selection also lacks specifics. Who will be recruiting the participants and through which methods? 3. Section on data collection would benefit from additional details a. A table providing specific clinical variables and their sources would be most helpful b. The methods of clinical data collection are also not clear. Will these data come from electronic health records collected by specialized computer programs, or will this be done by human data abstractors or perhaps a combination of the two methods? c. The sources of the ad hoc sections of the questionnaire (table 2) are not clear. Were these items previously published or used? Were

	they pilot tested or validated? 4. Data analysis plan is also rather rudimentary. The paper would be much stronger if the authors included one or two examples of specific hypotheses and then described the data elements and the specific analytic approaches used to test those hypotheses. 5. It is hard to judge the potential impact of the planned study without any information on the anticipated cohort size and statistical power. In the STROBE statement, item #10 is marked N/A. The authors are encouraged to provide at least a preliminary estimate of how many people are expected to be recruited. One minor point: The bolded text in the introduction looks strange. This is typically done for grant applications. The reader may be left wondering if some sections of the paper were copied and pasted from an earlier proposal.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Dr. P. Zarogoulidis, Aristotle Univ Thessaloniki Comments to the Author:
An excellent manuscript in its field, I have no corrections

We thank Dr. Zarogoulidis for taking the time to review our manuscript. Your compliments are much appreciated.

Reviewer 2

Dr. Michael Goodman, Emory University Rollins School of Public Health Comments to the Author:
Thank you for the opportunity to review this paper. Although the idea of creating a multicenter cohort of immunotherapy patients is praiseworthy, the description of the proposed study methods is somewhat vague. Below, I am offering a few suggestions that in my opinion will strengthen this paper.

We thank Dr. Goodman for taking the time to review our manuscript. We have provided our response to the comments and suggestions raised below.

1. I am afraid that a reader who only has time to review the abstract will come away without a clear understanding of the study design and its methods. For example, the abstract lacks a clear explanation of is meant by “a tailored questionnaire completed at regular intervals”, and the actual methods of data analysis are not mentioned.

Thank you for your comment. We have updated the methods section to better explain the design of the study. Since a broad variety of analyses will be performed, we try to briefly clarify but could not detail more.

Abstract, line 68-80: **:** *This international, observational, multi-centre study takes place in France, the Netherlands, Portugal and Spain. We aim to include about 1800 adult cancer patients treated with immunotherapy in a specifically recruited prospective cohort, and to additionally obtain data from historical real-world databases (i.e. databiobanks) and medical administrative registries (i.e. national cancer registries) in which relevant data regarding other adult cancer patients treated with immunotherapy has already been stored. In the prospective cohort, clinical health status, HRQoL and psychosocial well-being will be monitored until 18 months after treatment initiation through questionnaires (at baseline and 3, 6, 12 and 18 months thereafter), and by data extraction from electronic patient files. Using advanced statistical methods, including causal inference methods,*

artificial intelligence algorithms and simulation modelling, we will use data from the QUALITOP cohort to improve the understanding of the complex relationships between treatment regimens, patient characteristics, irAEs and HRQoL.

2. Section on Patient Selection also lacks specifics. Who will be recruiting the participants and through which methods?

Thank you for pointing this out. We have included the following statement under the header "Patient selection":

Page 8, lines 178-180*: "For the prospective cohort, patients will be asked to participate by trained members of the medical staff, such as doctors and (research) nurses, during visits that are part of regular care."*

3. Section on data collection would benefit from additional details

a. A table providing specific clinical variables and their sources would be most helpful

We agree that this would be of added value. We have included the table below in the supplements. It consists of an overview of domains and examples of clinical variables, all of which are extracted from electronic health records. We referred to this supplemental table in line 226-227 of the manuscript.

Domain	Examples
Baseline	
Patient demographics	Sex, month and year of birth, height
Cancer diagnosis	Cancer type (ICD-10), date of diagnosis, current stage (TNM/Lugano)
Past and current cancer treatment	Type of treatment (surgery, chemotherapy, targeted therapy, immunotherapy, radiotherapy), treatment line, start date, stop date, treatment medication, medication dose, number of cycles, best response, early treatment termination, reason for early treatment termination
Medical History	Relevant medical history (ICD-10) (e.g. cardiovascular diseases, neurological diseases, pulmonary diseases, diabetes, renal diseases, malignancies, auto-immune diseases), start date, end date
Current medication	medication type (according to Drug Ontology (DrOn), start date
Continuous monitoring	
Clinical examination	Date of examination, weight, temperature, heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, respiratory rate, ECOG performance status, response to treatment (RECIST/Lugano)
Blood analyses	Date of examination, CRP, glucose, creatinine, troponine, ASAT, ALAT, LDH, albumin, protein, sodium, potassium, leucocytes, erythrocytes, thrombocytes, neutrophils, eosinophils, lymphocytes, haemoglobin, TSH, FT4, cortisol
Adverse events	Adverse event type (CTCAE), adverse event grade (CTCAE), start date, end date, treatment

b. The methods of clinical data collection are also not clear. Will these data come from electronic health records collected by specialized computer programs, or will this be done by human data abstractors or perhaps a combination of the two methods?

The data collection relies on manual extraction from electronic health records. This has been clarified in the methods section.

Page 10, lines 207-209: *"Clinical data will be manually extracted from electronic patient files for both cohorts."*
Page 11, line 222: *"Clinical data will be manually extracted from electronic patient files for each routine visit in the first 6 months of treatment and at fixed timepoints in the following year (9, 12 and 18 months)."*

c. The sources of the ad hoc sections of the questionnaire (table 2) are not clear. Were these items previously published or used? Were they pilot tested or validated?

We thank the reviewer for pointing this out. The questionnaire as a whole was not pre-tested (because it was constructed during the Covid crisis and it was not possible to meet with patients). However, it has been reviewed by oncologists in all the countries involved in the data collection. For this purpose, the questionnaire was written in French (native language of the work package who created the questionnaire). It was then translated by a specialized company into English, Dutch, Portuguese and Spanish. The English version will not be used for the survey, but was created to facilitate the work of the researchers in an international context. When a validated scale existed in all (or severl) of the languages involved in the administration, then it was preferred and the validated versions were used. Validated scales that were not available in one or more languages were translated for administration (most often from English to other languages). Ad-hoc items were translated from French into all other languages.

The ad-hoc items of the questionnaire were constructed primarily based on expert opinions and prior experience with research in similar patient populations. In the development and evaluation of the ad hoc items, we relied on clinician's knowledge of immunotherapy and their experience in dealing with patients. We relied on this experience to create the items rather than on the literature as there was little available on immunotherapy at the time the questionnaire was constructed. We included the following information in the methods section:

We included the following information regarding the questionnaire development in the manuscript:

Page 12, lines 241-243: *"The questionnaire as a whole was not pre-tested (because it was constructed during the COVID-19 pandemic, and it was not possible to meet with patients). However, it was reviewed by oncologists in all the countries involved in the data collection."*

Page 14, lines 263-268: *"Ad-hoc items are used for domains for which no suitable validated questions/questionnaires were available. The items are based on expert opinions and prior experience with research in similar patient populations. Especially for domains 5 ("Medication and treatment") and 6 ("Opinions on cancer treatment and care"), clinicians' knowledge and experience with immunotherapy treatment was of key importance in developing and evaluating the ad hoc items."*

4. Data analysis plan is also rather rudimentary. The paper would be much stronger if the authors included one or two examples of specific hypotheses and then described the data elements and the specific analytic approaches used to test those hypotheses.

We acknowledge that the analytic strategies are not described in detail in the manuscript, owing to the diversity of hypotheses and methods that the QUALITOP project encompasses. For instance, the different parts of the project pertain to the three types of statistical goals: description, explanation and prediction. As such, we could not provide a complete description of the hypotheses and statistical approaches used. However, below is a specific example of the use of joint modelling to study the associations between ICI treatment and changes in health related QoL, using the OncoLifeS study (described in Table 1).

The data comes from the data biobank OncoLifeS which is a prospective cohort study conducted in University Medical Centre Groningen, Netherlands. We will include patients diagnosed with lung cancer, older than 18 years and receiving treatment with ICI for any given duration, who filled at least one questionnaire on QoL shortly before (<6 weeks), during or after their ICI treatment. The aim will be to study the associations between ICI treatment and changes in health related QoL in the two years after treatment initiation among patients diagnosed with lung cancer.

First, the evolution of the different components of QoL over time for individual patients will be described using spaghetti plots and boxplots. Then, joint models will be used to estimate the effect of ICI treatment on QoL over two years' time since the initiation of ICI treatment. The joint model has two components which allows the simultaneous study of longitudinal and time-to-event data. In this case, the model assesses repeated measurements of QoL individuals over time, as well as the competing risks represented by the expected time between ICI treatment initiation and death. The first component fits a generalised linear mixed effect model with a random effect accounting for repeated measurements and a random slope to account for inter-individual variations in trajectories over time. Adjusted mean differences along with their 95% confidence intervals will be reported for treatment effects. The validity of this mixed effects model will be checked by inspecting the diagnostic plots of the residuals. The other component of the joint model is the time-to-event model. To account for the competing risk of death, time to death from initiation of ICI treatment will be modelled using Cox proportional hazard models. The JM/JMBayes package in R used for fitting joint models only allow for Cox proportional hazard models for time-to-event analysis. Hence, we will assess the proportional hazards assumption using 1) non-parametric plots, 2) hypothesis tests for whether the effect of covariates on the hazard varies by time and 3) using plots of Schoenfeld residuals. The functional form of continuous covariates will be investigated using Martingale residuals and lastly, the overall model fit will be assessed using deviance residuals. All the models will be adjusted for a priori specified covariates, identified via directed acyclic graphs (DAG). All patient characteristics (e.g. demographics, tumour characteristics, comorbidities, cancer treatments) will be included as time-fixed in the model.

We have rephrased the first paragraph of the statistical analyses section to provide a little more context.

***Page 17, lines 323-329:** "We plan to use a broad variety of statistical methods for the purposes of description (e.g. describe baseline characteristics), explanation (e.g. explain changes in HRQoL by irAEs) and prediction (e.g. predict patients at risk for HRQoL deterioration through patient characteristics). In addition, we will use machine learning techniques and mapping methods to exploit fully the vast amount of collected data and provide a deep understanding of the causal mechanisms underlying HRQoL of patients treated with immunotherapy. A special focus lies on understanding the influence of adverse events and individual characteristics."*

5. It is hard to judge the potential impact of the planned study without any information on the anticipated cohort size and statistical power. In the STROBE statement, item #10 is marked N/A. The authors are encouraged to provide at least a preliminary estimate of how many people are expected to be recruited.

We understand your concern and have modified the abstract and the manuscript accordingly. The anticipated size of the prospective cohort was approximately 1800 patients. However, due to the COVID-19 pandemic, inclusion rates were majorly affected. We hope to overcome this with the six month extension we received from the European Union. Furthermore, we are making efforts to retrospectively enrich the historical databases that are part of QUALITOP as much as possible, for example by collecting additional clinical data from patients' medical records (if informed consent allowed this). Through these efforts, we've now realized a combined historic/prospective cohort of 1794 patients (of whom 676 patients are in the prspective arm). The inclusion of prospective patients is still ongoing.

***Abstract, line 69-74:** "We aim to include about 1800 adult cancer patients treated with immunotherapy in a specifically recruited prospective cohort, and to additionally obtain data from*

historical real-world databases (i.e. databiobanks) and medical administrative registries (i.e. national cancer registries) in which relevant data regarding other adult cancer patients treated with immunotherapy has already been stored."

Page 8, line 180-182: *"Based on the average number of eligible patients treated in the participating clinical centres, we aim to include about 1800 patients in the prospective cohort."*

One minor point: The bolded text in the introduction looks strange. This is typically done for grant applications. The reader may be left wondering if some sections of the paper were copied and pasted from an earlier proposal.

Thank you for pointing this out. However, we do not see any bolded text in the version of the manuscript we submitted. This may have happened in the online submission system, we will pay attention to this during resubmission.

VERSION 2 – REVIEW

REVIEWER	Goodman, Michael Emory University Rollins School of Public Health, Epidemiology
REVIEW RETURNED	09-Mar-2023

GENERAL COMMENTS	I am satisfied with the revisions. Thank you.